



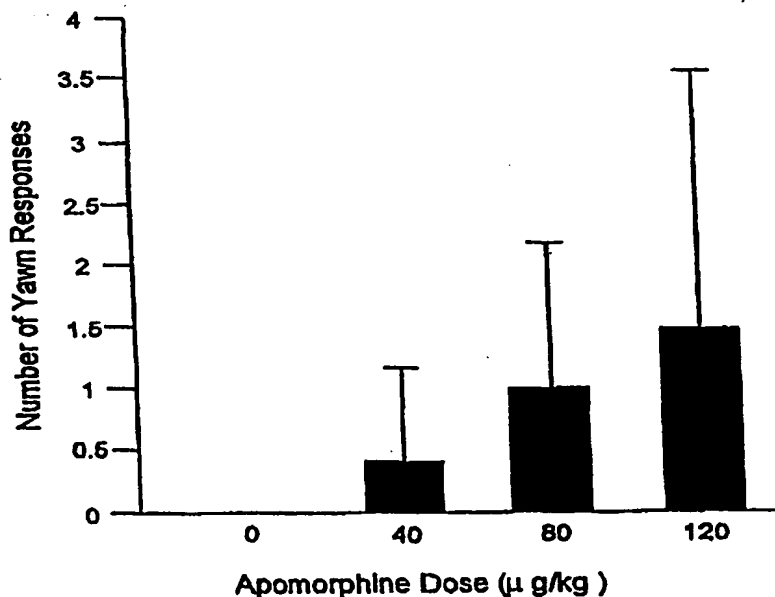
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/00		A2	(11) International Publication Number: WO 99/66909
			(43) International Publication Date: 29 December 1999 (29.12.99)
(21) International Application Number: PCT/CA99/00567 (22) International Filing Date: 21 June 1999 (21.06.99) (30) Priority Data: 09/102,987 22 June 1998 (22.06.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/102,987 (CIP) Filed on 22 June 1998 (22.06.98)		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published Without international search report and to be republished upon receipt of that report.	
(71) Applicant (for all designated States except US): QUEEN'S UNIVERSITY AT KINGSTON [CA/CA]; Kingston, Ontario K7L 3N6 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): ADAMS, Michael, A. [CA/CA]; 341 Renda Street, Kingston, Ontario K7M 5X9 (CA). HEATON, Jeremy, P., W. [CA/CA]; 1818 MacAlpine Road, R.R. #3, Gananoque, Ontario K7G 2V7 (CA). (74) Agents: STEEG, Carol, Miernicki et al.; Parteq Innovations, Queen's University at Kingston, Kingston, Ontario K7L 3N6 (CA).			

(54) Title: METHOD AND COMPOSITIONS FOR THE TREATMENT OR AMELIORATION OF FEMALE SEXUAL DYSFUNCTION

(57) Abstract

The present invention provides a method of treating sexual dysfunction in a female, including the vasculogenic symptoms of delayed vaginal engorgement, diminished vaginal lubrication, pain or discomfort with intercourse (dyspareunia), diminished vaginal sensation, diminished vaginal orgasm, diminished clitoral sensation or diminished clitoral orgasm, or of combating vaginal pain by stimulating peripheral pelvic nerve release of nitric oxide (NO). The method comprises administering to a female in need of such treatment a therapeutically effective amount of a compound which acts on a mid-brain pathway to increase blood flow to the ilio-hypogastric-pudendal artery bed and stimulate the release of nitric oxide (NO) from peripheral NANC nerve cells. The preferred compound for the method of this invention is apomorphine or one of its pharmaceutically acceptable salts, esters, or pro-drugs. Alternatively, the apomorphine is co-administered with an apomorphine-potentiating amount of an androgen, preferably testosterone either prior to, or concomitantly with, the administration of the apomorphine.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

METHOD AND COMPOSITIONS FOR THE TREATMENT OR AMELIORATION
OF FEMALE SEXUAL DYSFUNCTION

5

10

Field of the Invention

15

16

25

The present invention relates to methods of diagnosing, treating, or ameliorating sexual dysfunction in female mammals, including methods of treating delayed vaginal engorgement, diminished vaginal lubrication, pain or discomfort with intercourse (dyspareunia), diminished vaginal sensation, diminished vaginal orgasm, diminished clitoral sensation or diminished clitoral orgasm, or of treating vaginal pain by stimulating peripheral pelvic nerve release of nitric oxide (NO). The treatment methods of the present invention include the improvement in a female of the physiological state associated with sexual activity including appropriate vaginal lubrication, vaginal sensation, vaginal orgasm, or clitoral sensation, but in whom one of the above-mentioned abnormal conditions may not be present.

30

Background of the Invention

Sexual response in mammals is mediated by a balanced interplay between the sympathetic and parasympathetic nervous systems. Vasocongestion, or erectile tumescence in both the male and female, is largely mediated by parasympathetic (cholinergic) outflow, whereas orgasm is predominantly sympathetic (adrenergic).

Sexuality in human females encompasses multiple components including physiological, psychological, social and emotional factors. However, the first phase of the female sexual response is mediated by a combination of vasocongestive and neuromuscular events which include increased clitoral length and diameter, as well as increased vaginal lubrication, wall engorgement and increased luminal diameter.

The clitoris is the homologue of the penis, arising from the embryological genital tubercle. As a result, the two organs have similar structural and arousal response mechanisms. The clitoris consists of a cylindrical, erectile organ composed of three parts: the outermost glans or head, the middle corpus or body, and the innermost crura. The body of the clitoris consists of paired corpora cavernosa of about 2.5 cm in length and lacks a corpus spongiosum. During sexual arousal, blood flow to the corpora cavernosa of the clitoris cause their enlargement and tumescence.

The clitoris plays a major role during sexual activity in that it induces local autonomic and somatic reflexes causing vaginal vasocongestion, engorgement, and subsequent transduction, lubricating the introital canal making the

sexual act easier, more comfortable, and more pleasurable.

Vaginal wall engorgement enables a process of plasma transduction to occur, allowing a flow through the epithelium and onto the vaginal surface. Plasma transduction results from the rising pressure in the vaginal capillary bed during the sexual arousal state. In addition, there is an increase in vaginal length and luminal diameter, especially in the distal 2/3 of the vaginal canal.

The vaginal canal is lubricated primarily from a transudate originating from the subepithelial vascular bed passively transported through the interepithelial spaces sometimes referred to as intercellular channels. Additional moistening during intercourse comes from secretion of the paired greater vestibular or Bartholin's glands.

These events depend upon sufficient blood flow to these organs during sexual arousal, and a physiologic disorder which impairs this blood flow, resulting in female vasculogenic sexual dysfunction, can ultimately lead to or exacerbate a pre-existing psychological condition.

The arterial supply to the vagina is derived from an extensive network of branching vessels surrounding it from all sides. The anterior branch of the internal iliac artery continually bifurcates as it descends through the pelvis with a series of the newly generated vessel, each supplying the vagina to some degree. After giving off an obturator artery branch, the umbilical and the middle rectal arteries diverge off to supply a superior and inferior vesical artery, respectively. Between the umbilical and the mid-rectal branches there is generation of a uterine artery which further bifurcates to give the vaginal artery. The

internal pudendal and accessory pudendal artery also sends a branch. Finally the common clitoral artery sends a branch to the vaginal muscularis.

5 The main arterial supply to the clitoris is from the ilio-hypogastric-pudendal arterial bed. The internal pudendal artery is the last anterior branch of the internal iliac artery. Distally, the internal pudendal artery traverses Alcock's canal, a position of the obturator fascia and lies on the inner side in supposition to the ischio-
10 pubic ramis. In this latter location, the artery is susceptible to blunt perineal trauma. The internal pudendal artery terminates as it supplies the inferior rectal and perineal artery, which supplies the labia. The common clitoral artery continues to the clitoris. This artery
15 bifurcates into a dorsal clitoral artery and a cavernosal clitoral artery.

Based upon animal research, it has been found that central nervous system areas primarily implicated in sexual arousal include the medial pre-optic, anterior hypothalamic
20 region and related limbic-hippocampal structures of the brain.

Female sexual dysfunction which has its origin in abnormal arterial circulation into the vagina or clitoris during sexual stimulation may be considered a disorder of
25 arousal. This vasculogenic female sexual dysfunction may include such clinical symptoms as delayed vaginal engorgement, diminished vaginal lubrication, pain or discomfort with intercourse (dyspareunia), diminished vaginal sensation, diminished vaginal orgasm, diminished
30 clitoral sensation or diminished clitoral orgasm.

Moreover, traumatic injury to the ilio-hypogastric-pudendal arterial bed from pelvic fractures or blunt perineal trauma may also result in diminished vaginal/clitoral blood flow following sexual stimulation and fall into the vasculogenic dysfunction category.

Vaginal pain may derive from a general vaginal hyperalgesia or sensitivity to stimulation associated with coitus (dyspareunia) when there has been sufficient genital engorgement and lubrication.

Treatment of female sexual dysfunction is gradually evolving as more clinical and basic science studies are dedicated to the investigation of this medical problem. Female sexual complaints are not all psychological in pathophysiology, especially for those individuals who may have a component of vasculogenic dysfunction contributing to the overall female sexual complaint. Aside from hormone replacement therapy, medical management of female sexual dysfunction remains in the early phases of development. All non-hormonal medications listed below are undergoing safety and efficacy testing for the treatment of male erectile dysfunction and are only in the experimental stage for the treatment of female sexual dysfunction.

Estrogen replacement therapy is presently used in post-menopausal women (either spontaneous or surgical) for the treatment of hot flashes, prevention of osteoporosis, and diminishment of the risk of heart disease. Estrogen replacement results in improved clitoral sensitivity, increased libido and decreased pain/burning during intercourse. Local or topical estrogen application relieves symptoms of vaginal dryness, burning, urinary frequency and

urgency. No clinical evidence exists thus far that the use of topical estrogen cream results in relief of sexual complaints other than local vaginal pain or vaginal dryness.

5 Methyl testosterone may be used in combination with estrogen in post-menopausal women for symptoms of inhibited desire, dyspareunia or lack of vaginal lubrication. Topical vaginal testosterone is used for treatment of vaginal lichen planus. These women, usually elderly, are noted to have clitoral enlargement, increased facial hair and increased sexual appetite. There are conflicting reports regarding the benefit of methyl testosterone for the treatment of inhibited desire and/or vaginismus in pre-menopausal women.

10 In men, topical application of prostaglandin E1 combined with a skin enhancer such as SEPA is presently demonstrating initial success in pilot Phase II clinical trials. Clinical studies are necessary to determine the safety and efficacy of this medication used as a topically-administered vaginal vasoactive agent in the treatment of vasculogenic female dysfunction. However, one study has demonstrated increased clitoral blood flow and clitoral erection following local prostaglandin E1 injection into clitoral corporal erectile tissues.

15 Sildenafil functions as a selective type 5 (i.e. c-GMP specific) phosphodiesterase inhibitor, and acts to decrease the metabolism of c-GMP, the second messenger in nitric oxide mediated male erectile response. An oral formulation of this medication has proven to be safe and effective in improving erectile duration and rigidity. In females, nitric oxide/NOS exists in human vaginal and clitoral tissue. Sildenafil may prove useful alone, or possibly in

20
25
30

-7-

combination with other vasoactive agents for the treatment of vasculogenic female sexual dysfunction. Clinical studies evaluating the efficacy of this medication in women are needed.

5 Phentolamine is currently available as an oral preparation with rapid absorption and metabolism. Phentolamine's mechanism of action inducing vascular smooth muscle relaxation occurs via alpha-adrenergic blockade as well as by direct smooth muscle relaxation. Studies are
10 currently in progress using this medication in women with female sexual dysfunction.

 Despite these advances in the discovery of agents effective to treat female sexual dysfunction, there still exists a need for the discovery of additional compounds
15 useful in the treatment of this condition.

Summary of the Invention

 In one embodiment, the present invention provides a method of treating or ameliorating sexual dysfunction in female mammals by administering to a mammal in need of such treatment a therapeutically effective amount of a compound which acts upon mid-brain pathways to increase blood flow to the ilio-hypogastric-pudendal arterial bed and genitalia.

 In another embodiment, the present invention provides a
25 method of combating vaginal pain by administering to a mammal in need of such treatment a therapeutically effective amount of a compound which acts upon mid-brain pathways to stimulate peripheral nerve release of nitric oxide (NO) in the pelvic nerve network, preferably from non-adrenergic,
30 non-cholinergic (NANC) nerves. The vaginal pain may be

general hyperalgesia (non-specific increased vaginal sensitivity) or pain associated with intercourse (dyspareunia).

5 The selected compound is one which acts upon any of the mid-brain pathways which include the dopaminergic, serotonergic, oxytocinergic or nitroxidergic mid-brain pathways.

10 In another embodiment, the present invention provides a method for producing an effective vasocongestive arousal in a female comprising administering a therapeutically effective amount of a compound which acts upon a mid-brain dopaminergic, serotonergic, oxytocinergic or nitroxidergic pathway to increase blood flow to the ilio-hypogastric-pudendal arterial bed and genitalia. By effective
15 vasocongestive arousal is meant clitoral erection, vaginal and labial engorgement, and lubrication adequate for intercourse.

20 In yet another embodiment, the present invention provides a means of treating vaginal engorgement insufficiency in a female mammal comprising administering a therapeutically effective amount of a compound which acts upon a mid-brain dopaminergic, serotonergic, oxytocinergic or nitroxidergic pathway to increase blood flow to the ilio-hypogastric-pudendal arterial bed and genitalia.

25 In another embodiment, the present invention provides a method of treating clitoral erectile insufficiency in a female mammal comprising administering a therapeutically effective amount of a compound which acts upon a mid-brain dopaminergic, serotonergic, oxytocinergic or nitroxidergic
30 pathway to increase blood flow to the ilio-hypogastric-

pudendal arterial bed and genitalia.

In still another embodiment, the present invention comprises a method of treating dyspareunia in a female mammal comprising administering a therapeutically effective amount of a compound which acts upon a mid-brain dopaminergic, serotonergic, oxytocinergic or nitroxidergic pathway to facilitate peripheral nerve release of NO in the pelvic nerve network, preferably from non-adrenergic, non-cholinergic nerves.

In the embodiments described above, an androgen may optionally be co-administered with the primary active compound, wherein co-administration of the androgen enhances or potentiates the effect of the principal therapeutic agent.

In yet another embodiment, the present invention provides a means of diagnosing the presence or absence of sexual dysfunction in a female mammal. The diagnostic method comprises the steps of administering apomorphine alone or in combination with an androgen and observing any change in physiologic response associated with sexual activity. A change indicates the presence of sexual dysfunction.

Brief Description of the Drawing

IN THE DRAWING:

FIGURE 1 is a histogram depicting yawning response of female test animals following administration, in a first study, of various doses of apomorphine.

FIGURE 2 is a histogram depicting yawning response of female test animals administered, in a second study, equal 80 microgram/kg doses of apomorphine at various times following the pre-administration of equal 480 microgram/kg doses of testosterone.

FIGURE 3 is a graph showing blood levels of estrogen and progesterone in the female rat during various stages of the rat estrous cycle.

FIGURE 4 is a histogram depicting genital licking and yawn response data from a third study in which female rats were administered either saline or 80 micrograms/kg of apomorphine during either the proestrus/estrus or metestrus/diestrus stages of the estrous cycle.

FIGURE 5 presents histograms depicting genital licking and yawn response data from a fourth study in which female rats were pre-administered 480 microgram/kg doses of testosterone 36 hours prior to the administration of saline or apomorphine during a particular stage of the estrous cycle. The data compare responses in the proestrus/estrus and the metestrus/diestrus stages following administration of testosterone and either saline or apomorphine.

FIGURES 6 and 7 are histograms showing genital lick and yawn response data, respectively, from a study in which female rats were administered either saline or apomorphine, with or without the prior administration

-11-

of testosterone. Data are presented for both the proestrus/estrus and metestrus/diestrus stages of the estrous cycle.

FIGURE 8 is a histogram comparing genital lick and yawn response data which compare the data from the studies where either saline or an 80 microgram/kg dose of apomorphine was administered to test animals with and without prior administration of a 480 microgram/kg dose of testosterone.

FIGURES 9 and 10 are histograms presenting genital lick and yawn response data, respectively, comparing intact animals administered control or saline during the metestrus/diestrus stage of the rat estrous cycle with ovariectomized animals administered a corresponding regimen of drug or control.

Detailed Description

As used throughout this specification and the appended claims, the following terms have the meanings ascribed to them.

By "androgen" is meant any compound recognized in the art to elicit an androgenic effect, either in their free base form or in the form of a salt or pro-drug by acting on androgen receptors in an agonist-like manner. Also included in the definition of "androgen" is any compound which mimics an art-recognized androgen, which compound stimulates or activates androgenic pathways. Representative androgens include testosterone, dihydrotestosterone (DHT), dehydro-

epiandrostenedione (DHEA), and dehydroepiandrostenedione sulfate (DHEAS).

The terms "acute dose" or "acute administration" of a drug mean the scheduled administration of a drug to a patient on an as-needed basis at a dosage level determined by the attending physician to elicit a relatively immediate desired reaction in the patient, given the patient's age and general state of health.

A "sub-acute dose" is a dose of the drug at a lower level than that determined by the attending physician to be required for an acute dose, as described above. Sub-acute doses may be administered to the patient on an as-needed basis, or in a chronic, or on-going dosing regimen.

The terms "continuous dose" or "chronic administration" of a drug mean the scheduled administration of a drug to the patient on an on-going day-to-day basis.

The term "co-administration" of two or more drugs denotes the simultaneous acute dosing of the drugs, or the sequential administration of two or more drugs with a period of delay between their administration. One drug may be administered in a chronic dose, with the other drug(s) administered on an acute or as-needed basis.

By the term "treatment of sexual dysfunction" is meant the treatment, prevention, or amelioration of the conditions of delayed vaginal engorgement, diminished vaginal lubrication, pain or discomfort with intercourse (dyspareunia), diminished vaginal sensation, diminished vaginal orgasm, diminished clitoral sensation, diminished clitoral orgasm, or generalized vaginal pain. In addition, the term "treating sexual dysfunction," as contemplated in

this application, means the improvement in a female of the physiological state associated with sexual activity which includes appropriate vaginal lubrication, vaginal sensation, vaginal orgasm, or clitoral sensation, but in whom one of the above-mentioned abnormal conditions may not be present.

It is to be understood that the determination of the appropriate dose regimen for a given patient is well within the skill of the attending physician. Since the proper dose varies from person to person based on the age and general state of health, it is a common practice of physicians to "dose-titrate" the patient; that is, to start the patient on a dosing regimen which is at a level below that required to produce the desired response, and gradually increase the dose until the desired effect is achieved.

The term "effective vasocongestive arousal" means, in the female, tumescent clitoral erection, engorgement, swelling and lubrication of the vagina and engorgement and swelling of the labia. Such arousal conditions may result from a net increase in blood flow to genital tissues caused by (a) increased inflow with normal outflow, (b) increased inflow with decreased (vasoconstricted) outflow, or (c) normal inflow with decreased outflow.

Compounds useful in the methods of the present invention are those compounds which are known to act upon the mesencephalon or mid-brain nerve pathways to increase blood flow to the ilio-hypogastric-pudendal arterial bed and genitalia or to act on a mid-brain neural pathway to stimulate vasodilation, and genital engorgement and lubrication. This action may be by, for example, peripheral release of nitric oxide (NO) from non-adrenergic,

non-cholinergic (NANC) nerve cells in the pelvic region. Examples of these compounds include those which are known to act on any of the dopaminergic, serotonergic, oxytocinergic or nitroxidergic mammalian mid-brain pathways to produce such peripheral effects.

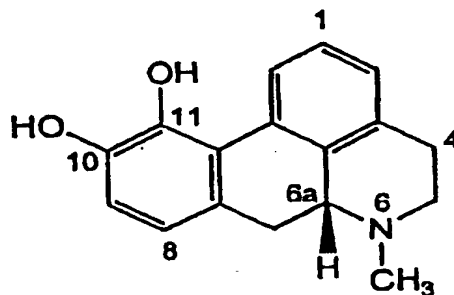
Dopaminergic pathway compounds include apomorphine, bromocriptine, lisuride, methergoline, pergolide, piribidil, and quinpirole.

Serotonergic pathway compounds include serotonin receptor agonists such as 1-(2,5-dimethoxy-4-iodophenyl)-laminopropane, 5-methoxytryptamine, α -methyl-5-hydroxytryptamine, 2-methyl-5-hydroxytryptamine, N-acetyl-5-hydroxytryptamine buspirone, and sumatriptan.

Oxytocinergic pathway compounds include oxytocin analogues such as isotocin, carbetocin, Lys-conopressin, deaminoxytocin, mesotocin, antocin, glumitocin, aspartitocin, valitocin, asvatocin, phasvatocin, and seritocin.

The preferred compound for use in the methods of the present invention is apomorphine or one of its salts, esters or pro-drug forms. Apomorphine, (R)-5,6,6a,7-tetrahydro-6-methyl-(4H)-dibenzo[de,g]quinoline-10,11-diol, is a derivative of morphine obtained by treatment of the latter with concentrated hydrochloric acid (L. Small, et al., J. Org. Chem., 5: 334 (1940)) or by heating morphine with zinc chloride (Mayer, Ber., 4: 171 (1871)). The compound has the chemical structure shown below and possesses a chiral center at position 6a. The total synthesis of the racemic mixture is reported by J. L. Neumeyer, et al., J. Pharm. Sci., 59:1850 (1970) and the synthesis of the separate enantiomers

by V. J. Ram and J. Neumeyer, J. Org. Chem., 46: 2830 (1981).



The compound possesses a basic nitrogen atom at position 6 and is thus capable of existing in the free base form as well as acid addition salt forms. The compound may be administered as the free base or in the form of one of its pharmaceutically acceptable salts or pro-drug derivatives.

As used herein, the term "pharmaceutically acceptable salt" refers to those salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 66: 1-19 (1977). The salts are prepared *in situ* during the final isolation and purification of the compounds of the invention, or separately by reacting the free base function with a suitable organic acid. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an

amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid or malonic acid or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like.

The term "pro-drug" refers to compounds that are rapidly transformed in vivo to yield the parent compound, as for example, by hydrolysis in blood. T. Higuchi and V. Stella provide a thorough discussion of the pro-drug concept in "Pro-drugs as Novel Delivery Systems", Vol. 14 of the A.C.S. Symposium Series, American Chemical Society (1975). Examples of esters useful as pro-drugs for compounds containing carboxyl groups may be found on pages 14-21 of "Bioreversible Carriers in Drug Design: Theory and Application," edited by E.B. Roche, Pergamon Press (1987).

-17-

The term "pro-drug ester group" refers to any of several ester-forming groups that are hydrolyzed under physiological conditions. Examples of pro-drug ester groups include pivoyloxymethyl, acetoxymethyl, phthalidyl, indanyl and methoxymethyl, as well as other such groups known in the art.

As used herein, the term "pharmaceutically acceptable ester" refers to esters which hydrolyze in vivo and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanolic, alkenolic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include formates, acetates, propionates, butyates, acrylates and ethylsuccinates.

Apomorphine has been shown to be effective in facilitating and maintaining erectile response in males. Formulations containing apomorphine for this purpose, and methods of treating erectile dysfunction in males is disclosed in United States Patent 5,770,606, the entire contents of which are incorporated herein by reference.

The studies which are presented below illustrate that apomorphine also enhances the sexual response in females, with its effect being potentiated by co-administration of an androgen. The preferred androgen is testosterone or one of its pharmaceutically acceptable salts, esters or pro-drugs.

For an optimal vasocongestive arousal response in the female, steady state circulating serum and mid-brain tissue

-18-

levels of apomorphine should be maintained within a relatively closely defined range. The drug is preferably administered in a formulation which delivers the drug to the system while maintaining and not exceeding the desired systemic levels of the drug. Methods known to the practitioner of the pharmaceutical formulation arts which accomplish this may be used. For example, the drug may be delivered to the system by means of a solid oral formulation, by a liquid formulation, including one applied sub-lingually; by a tablet, lozenge, or lollipop held in the mouth and absorbed buccally; by means of a suppository formulation administered intravaginally or rectally; by a powder, gel, or suspension, or an intra-nasal spray formulation. Formulations for the intra-nasal administration of apomorphine are taught, for example, in United States Patent 5,756,483 to Merkus; buccal or sub-lingual formulations for the administration of apomorphine are taught in United States Patent 5,888,534 to El-Rashidy, et al. The teachings of both patents are incorporated herewith by reference.

The drug may also be administered in a sterile parenteral formulation by sub-cutaneous or intramuscular route, although sub-lingual, buccal, intra-nasal, and suppository formulations are preferred because of their greater ease of administration and the resulting greater potential for patient acceptance.

Sublingual dosage forms, usually containing about 1 to about 12 milligrams, preferably about 2.5 to about 10 milligrams of apomorphine, are useful in treating the symptoms of female vasculogenic sexual dysfunction,

including its symptomatic manifestations without nausea or other undesirable side effects. Plasma concentrations of apomorphine are preferably at between about 0.1 to 6 nanograms per milliliter, preferably between about 0.3 to about 4 nanograms per milliliter, and more preferably between about 1 to about 2 nanograms per milliliter, sufficient to induce clitoral erection, vaginal and labial engorgement and lubrication adequate for intercourse (i.e. "effective vasocongestive arousal") but less than the amount that induces nausea.

The apomorphine is administered in the time period immediately prior to sexual activity, generally during the period between about 2 minutes and 120 minutes prior to sexual activity, preferably during the period between about 2 minutes and about 60 minutes prior to sexual activity, so as to achieve desired serum and mid-brain tissue levels of the drug.

Apomorphine has been recognized for use as an emetic when administered subcutaneously in about a 5-milligram dose. For the purposes of the present invention, apomorphine or a similarly acting dopamine receptor agonist is administered in an amount sufficient to excite cells in the mid-brain region of the patient but with minimal side effects. This cell excitation is believed to be part of a cascade of stimulation that is likely to include neurotransmission with serotonin and oxytocin.

The dopamine receptors in the mid-brain region of a patient can be stimulated to a degree sufficient to cause an erectile response by the administration, preferably sublingually, of apomorphine so as to maintain a plasma

concentration of apomorphine of no more than about 5.5 nanograms per milliliter (5.5 ng/ml). The sublingual administration usually takes place over a time period in the range of about 1 to about 10 minutes, or longer. The amount of apomorphine administered sublingually over this time period is preferably in the range of about 10 micrograms per kilogram ($\mu\text{g/kg}$) of body weight to about 100 $\mu\text{g/kg}$ of body weight, more preferably from about 25 $\mu\text{g/kg}$ to about 80 $\mu\text{g/kg}$ of body weight.

Co-administration of an androgen potentiates the effect of apomorphine in eliciting sexual arousal, as shown in the studies described below. Representative suitable androgens for co-administration with apomorphine in the methods of the present invention include testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), and pharmaceutically acceptable salts, esters and pro-drugs of the foregoing, including testosterone undecanoate and dehydroepiandrosterone sulfate (DHEAS).

The androgen is co-administered with the apomorphine, in one alternative dosing regimen, simultaneously, with both drugs being administered in acute doses, or with the apomorphine being administered in an acute dose, with the androgen administered in a sub-acute dose. Alternatively, the androgen may be administered at a chronic low dose, with the apomorphine administered in an as-needed dose, or with the apomorphine administered chronically, with the androgen administered on an as-needed basis.

Sustained release formulations for administration of a chronic low-dose of the androgen may take the form of well-known depot formulations, esters or pro-drugs which undergo

-21-

bioconversion to release the androgen, or trans-dermal patch formulations.

In the studies shown below, the potentiating influence of an androgen on the sexual arousal effects of apomorphine in female rats were found to be maximal when the androgen was administered about thirty-six hours prior to the administration of apomorphine. However, this delayed effect may have been due to pharmacokinetic effects associated with the mode of delivery or the form of the drug employed. However, these data suggest that slower-acting forms of androgen should be administered in the interval between about 2 to about 48 hours prior to the administration of apomorphine. The androgen may be made more readily available by administration in a form which delivers the drug to the blood stream more rapidly. This can be achieved by direct application of the androgen to mucosal tissue, such as by rectal, vaginal, intranasal, buccal, or sublingual administration. When a faster-acting form of androgen is employed, the the androgen may be administered in the period 2-hours prior to administration of the apomorphine, or concomitantly therewith.

In one alternative dosing regimen for co-administering an androgen and apomorphine to humans, the androgen is administered in an oral dosage form prior to the apomorphine, as in a pill, tablet, lozenge, or capsule form. In a second alternative dosing regimen, the androgen is administered in a rapidly-available form concomitantly with the apomorphine.

Andriol, (Organon, 375 Mt. Pleasant Ave., West Orange, NJ 07052) is a rapidly available oral dosage form of

testosterone undecanoate packaged as an oil solution sealed in capsules. This formulation rapidly delivers testosterone by bypassing the liver and making the testosterone available through the lymphatic system.

5 The present invention thus contemplates, in one embodiment, a combination package having unit dosage forms of both apomorphine and an androgen, preferably testosterone. Both dosage forms may be in the form of rapidly acting doses of the two drugs, such as testosterone
10 undecanoate described above, and a buccal, sub-lingual, or intra-nasal dosage form of apomorphine.

Illustrative preferred sublingual dosage forms of apomorphine are set forth in Table I, below.

TABLE I

150-Milligram Apomorphine Hydrochloride
Sublingual Tablets

3-mg Tablet

20	Apomorphine Hydrochloride	2.00 wt-%
	Mannitol	66.67 wt-%
	Ascorbic Acid	3.33 wt-%
	Citric Acid	2.00 wt-%
	Avicel PH 102	15.00 Wt-%
25	Methocel E4	10.00 Wt-%
	Aspartame	0.67 wt-%
	Magnesium stearate	0.33 wt-%

-23-

4-mg Tablet

Apomorphine Hydrochloride	2.65 wt-%
Mannitol	66.00 wt-%
Ascorbic Acid	3.33 wt-%
5 Citric Acid	2.00 wt-%
Avicel PH102	15.00 wt-%
Methocel E4M	10.00 wt-%
Aspartame	0.67 wt-%
Magnesium stearate	0.33 wt-%

5-mg Tablet

Apomorphine Hydrochloride	3.33 wt-%
Mannitol	65.34 wt-%
Ascorbic Acid	3.33 wt-%
15 Citric Acid	2.00 wt-%
Avicel PH102	15.00 wt-%
Methocel E4M	10.00 wt-%
Aspartame	0.67 wt-%
Magnesium stearate	0.33 wt-%

If desired, and in order to facilitate absorption and thus bioavailability, the presently contemplated dosage forms can also contain, in addition to tableting excipients, β -cyclodextrin or a β -cyclodextrin derivative such as hydroxypropyl- β -cyclodextrin (HPBCD). Illustrative dosage forms containing HPBCD are shown in Tables II and III, below.

TABLE II

Apomorphine Hydrochloride Sublingual Tablets
With Hydroxypropyl- β -Cyclodextrin

		<u>mg/Tab</u>
5	Apomorphine hydrochloride	4.0
	HPBCD	5.0
	Ascorbic acid	10.0
	PEG 8000	39.5
10	Mannitol	39.5
	Aspartame	<u>2.0</u>
	Total	100.0

TABLE III

Apomorphine Hydrochloride Sublingual
Tablets With β -Cyclodextrin

		<u>mg/Tab</u>
20	Apomorphine hydrochloride	5.0
	β -Cyclodextrin	20.0
	Ascorbic acid	5.0
	Mannitol	68.9
	Magnesium stearate	1.0
25	D&C Yellow 10 aluminum lake	<u>0.1</u>
	TOTAL	100.0

The onset of nausea can be obviated or delayed by
delivering apomorphine at a controlled dissolution rate so
as to provide circulating serum levels and midbrain tissue

levels of apomorphine sufficient for an effective vasocongestive arousal without inducing nausea. When apomorphine is administered at or near the relatively higher amounts of the aforementioned dosage range, the likelihood of nausea onset can be reduced by concurrent administration of a ganglionic agent (inhibitor of ganglionic response) such as nicotine or lobeline sulfate. For this purpose, the weight ratio of apomorphine to ganglionic agent is in the range of about 10 to about 1.

Other antiemetic agents that can be used in conjunction with apomorphine are antidopaminergic agents such as metoclopramide, and the phenothiazines, e.g., chlorpromazine, prochlorperazine, pipamazine, thiethylperazine, oxypendyl hydrochloride, and the like. Also suitable are the serotonin (5-hydroxytryptamine or 5-HT) antagonists such as domperidone, ondansetron (commercially available as the hydrochloride salt under the designation Zofran®), and the like, the histamine antagonists such as buclizine hydrochloride, cyclizine hydrochloride, dimenhydrinate (Dramamine), and the like, the parasympathetic depressants such as scopolamine, and the like, as well as other anti-emetics such as metopimazine, trimethobenzamide, benzaudinamine hydrochloride, diphenidol hydrochloride, and the like.

Nicotine-containing dosage forms and domperidone-containing dosage forms are illustrated in Table IV, below.

-26-

TABLE IV

Apomorphine Hydrochloride Sublingual Tablets
Containing an Anti-Emetic Agent

	<u>mg/Tab</u>
Apomorphine Hydrochloride	5.0
Ascorbic Acid	5.0
Mannitol	67.9
Magnesium Stearate	1.0
Nicotine	1.0
β -Cyclodextrin	20.0
D&C Yellow aluminum lake	<u>0.1</u>
TOTAL	100.0

	<u>mg/Tab</u>
Apomorphine Hydrochloride	5.0
Ascorbic Acid	5.0
Mannitol	58.9
Magnesium Stearate	1.0
Domperidone	10.0
β -Cyclodextrin	20.0
D&C Yellow 10 aluminum lake	<u>0.1</u>
TOTAL	100.0

The preferred sublingual dosage forms dissolve within a time period of at least about 2 minutes but less than about 10 minutes. The dissolution time can be longer, however, if desired as long as the desired plasma concentration of

-27-

apomorphine can be achieved. More preferably, the dissolution time in water for the presently contemplated dosage forms is about 3 minutes to about 5 minutes.

The present invention is illustrated further by the following studies. In the studies described below, the sexual behavior responses that were quantified were yawns and genital licks (the analogous female rat response to penile erections in the male rat). An event was counted as a genital lick when the animal stood on its hind legs, and rapidly and decisively descended (with a concavity of the back) into the genital area and proceeded to lick it. The yawn response is a direct indication of central activation of dopaminergic receptors by a drug (e.g. apomorphine). This pathway is at least in part convergent with the pathway which generates sexual responses. The yawns thereby represent a surrogate marker of sexual response. An event was counted as a yawn when the animal exhibited an involuntary opening of the mouth with the appropriate respiratory movement.

Female Wistar rats (Charles River Laboratories, (251 Ballardvale Street, Wilmington, MA 01887-1000, USA) utilized in the studies were housed, prior to each experiment, in plastic shoe-box cages in a climate-controlled room with a 12-hour light/12-hour dark cycle. The rats were allowed free access to food and water except during times of testing. During each test, the rats were placed in hanging cages fitted with Plexiglas® bottoms, in a dark, quiet room where they were allowed to acclimate for 10 minutes. After this period either drug or physiological saline (control) was injected subcutaneously to the back of the neck and

subsequent genital licking and yawning responses were observed for 30 minutes from a separate room via a video monitoring system. The standard deviations for both types of responses was determined, and statistical significance was determined using the Student's t-test with $p < 0.05$.

All experimental procedures were carried out in accordance with the guidelines established by the Canadian Council of Animal Care. Prior to any testing, each animal was handled by the investigator intermittently for 5 days to allow for acclimation by the animals to handling.

A stock solution of apomorphine hydrochloride, containing the drug at a concentration of 120 micrograms/mL, with 100 micrograms/mL of ascorbic acid in physiological saline, was prepared. The flask containing the mixture was covered with foil paper to prevent any light-induced decomposition and stored in refrigerator until used.

Testosterone propionate (Aldrich Chemical Co., Milwaukee, WI, USA) was diluted from a stock solution of 100mg/ml and dissolved in peanut oil prior to sub-cutaneous administration to animal.

In a first pilot study, randomized blind testing was performed with apomorphine doses of 40 micrograms/kg, 80 micrograms/kg, and 120 micrograms/kg, using saline for control. Doses were obtained by administering different amounts of the stock solution of 120 micrograms/mL. The results are presented in Figures 1 and 2 where Figure 1 shows a dose-dependent yawning response in the test animals.

In a second study, the potentiating influence of an androgen, testosterone, on the effects of apomorphine on sexual response in female rats was observed. Testosterone

was administered at a dosage of 480 micrograms/kg, with 80 microgram/kg doses of apomorphine being subsequently administered at times 0, 24, 36 and 48 hours following administration of the testosterone. The results are shown in Figure 2 where it was observed that the maximum number of apomorphine-induced yawing responses were observed when apomorphine was administered 36 hours following testosterone administration.

A third study was conducted to determine the effect of administering apomorphine during the various stages of the female rat's estrous cycle. As shown in Figure 3, the female rat's cycle is divided into 4 stages totaling approximately 4 days: proestrus, estrus, metestrus and diestrus. Estrogen levels are high prior to and at the beginning of proestrus, while progesterone levels are high at the end of proestrus. Both of these hormones are at low levels in metestrus and most of diestrus. Estrogen and progesterone are suggested to exert their fullest influence not until at least 24 hours after secretion. As a consequence, estrogen exerts its fullest influence during the proestrus and estrus stages while progesterone exerts its maximum influence during the metestrus and early diestrus stages.

In this study, physiological saline solution or 80 microgram/kg doses of apomorphine were sub-cutaneously administered to intact Wistar rats during either the proestrus/estrus stages or the metestrus/diestrus stages of their cycle. The stages for each animal were determined by examining the epithelial cell type in vaginal smears after the method of Baker, et al., "The Laboratory Rat", Vols. 1-

2, Academic Press, 1979. The observed licking and yawn response data are depicted in the histograms appearing in Figure 4. Apomorphine elicited a significant increase ($p < 0.05$) in yawns in the estrogen-influenced proestrus/estrus stages when compared with saline (control). However, no statistically significant effect was seen over control in inducing yawns in the progesterone influenced metestrus/diestrus stages. Apomorphine caused an increase, albeit not statistically significant, in genital licking responses in the proestrus/estrus stages, but no observed difference over control in the metestrus/diestrus stages.

In a fourth study, physiological saline solution (control) or 80 microgram/kg doses of apomorphine were administered to intact female Wistar rats during either the estrogen-influenced proestrus/estrus stages or the progesterone-influenced metestrus/diestrus stages, following prior administration of a 480 microgram/kg dose of testosterone. The results of the second study had shown that the potentiating influence of testosterone on the effects of apomorphine were maximal at around 36 hours after testosterone administration. Thus, in this study, administration of apomorphine to a test animal was timed to fall into the proestrus/estrus stages or the metestrus/diestrus stages of the animal's cycle at the appropriate time following administration of testosterone.

The genital lick and yawn response data for this study are depicted graphically in Figure 5. The data show that testosterone pre-treatment normalized the licking response in the female rat regardless of the hormonal state of the animal, or whether it was apomorphine or saline that was

-31-

administered. However, testosterone pre-treatment increased the yawn responses in those animals to which apomorphine was administered, compared with those that received saline (control).

5 Figure 6 depicts genital lick data comparing the administration of doses of 80 microgram/kg doses of apomorphine or physiological saline solution to two groups of intact Wistar rats to which testosterone was either pre-administered (striped bars) or not (open bars). The
10 corresponding data for yawn responses appears in Figure 7.

Referring to Figure 6, it can be seen that testosterone pre-treatment increased the observed number of genital licks in apomorphine-treated animals and saline-treated animals in the metestrus/diestrus stages when compared to (a) animals
15 treated with apomorphine and saline in the proestrus/estrus stages or (b) animals given no testosterone pre-treatment and apomorphine during the proestrus/estrus stages.

Referring to Figure 7, pre-treatment of test animals with testosterone also showed a larger increase over control in the number of observed yawn responses in apomorphine-treated animals during the metestrus/diestrus stages when
20 compared to the increase over control in testosterone pre-treated animals given apomorphine during the proestrus/estrus stages.

25 To study the effect of testosterone pre-treatment in animals which had considerably diminished levels of endogenous hormones, a fifth study was conducted in which the prior experiments were repeated with ovariectomized female Wistar rats. Rats were ovariectomized one month
30 prior to the experiments to ensure there was a minimal level

of endogenous hormones (estrogen and progesterone) present in the body. Ovariectomization involved the removal of the ovaries by severing the junction between the fallopian tube and uterine horn after the method detailed by Waynforth, H. and Flecknell, P., "Experimental and Surgical Technique in the Rat," St. Edmundsbury Press, Ltd., 1992. Rats that underwent this procedure were given ketamine and xylazine pre-operatively as anesthetics and 2 doses of 0.1 mL of the antibiotic Tribriksen 24% (Schering Canada, Inc.) and Buprenex for post-operative analgesia respectively. The animals were pre-administered a sub-cutaneous 480 microgram/kg dose of testosterone 36 hours prior to the administration of physiological saline solution or an 80 microgram/kg dose of apomorphine at the appropriate stage of the estrous cycle.

The genital lick and yawn response data for this experiment are shown graphically in Figure 8. As can be seen in Figure 8, the largest number of genital lick responses was seen in ovariectomized animals to which both testosterone and apomorphine had been administered. The effects of apomorphine alone over control or apomorphine in combination with testosterone over control in eliciting yawn responses is dramatic.

This study is informative with regard to the administration of combinations of testosterone and apomorphine to alleviate sexual dysfunction or normalize sexual function in post-menopausal women or in pre-menopausal women in which the hormonal milieu altered. The altered levels of endogenous hormones in such women are modeled by the ovariectomized rat. The dramatic

potentiating influence on the sexual arousal effects of co-administering androgen and apomorphine in the ovariectomized rat strongly suggest the efficacy of the use of this combination in the treatment of post-menopausal women and pre-menopausal women in whom the hormonal milieu is altered. The present invention thus includes the method of inducing effective vasocongestive arousal in such women by co-administering a therapeutically effective dose of apomorphine and an apomorphine-potentiating effective amount of androgen.

Figure 9 depicts graphically a comparison of data for intact animals administered apomorphine (with and without testosterone pre-treatment) to ovariectomized animals administered apomorphine (with and without testosterone pre-treatment). The data for the intact animals is shown for the metestrus/diestrus stages, since it is during these stages of the estrus cycle that endogenous hormonal levels are lowest in the intact animals, making for a fairer comparison with ovariectomized animals. As can be seen from Figure 9, there was no significant difference in genital lick responses between ovariectomized and intact animals, with the exception that in the trial where the animals were administered apomorphine alone.

Figure 10 depicts graphically the corresponding yawn response data comparing the intact and ovariectomized animals. The foregoing data show a marked increase in the apomorphine-treated ovariectomized animals compared with intact animals. The same marked difference in yawn responses is seen in the testosterone- and apomorphine-treated animals.

The foregoing data indicate that apomorphine is effective in initiating a sexual response in female rats. Moreover, the studies show that this sexual response is highly dependent upon hormonal levels of estrogen, progesterone and testosterone, with estrogen and testosterone having a potentiating influence on the effect of apomorphine and progesterone having an inhibitory influence.

The foregoing discussion and the reported studies are intended as illustrative of the present invention and are not to be read as limiting the invention as it is defined by the appended claims.

WE CLAIM:

1. A method of treating sexual dysfunction in a female mammal in need of such treatment which comprises
5 administering to said female a therapeutically effective amount of a compound which acts upon a mid-brain pathway to increase blood flow in the ilio-hypogastric-pudendal arterial bed and genitalia.
- 10 2. The method of Claim 1 wherein said compound acts upon a mid-brain dopaminergic pathway.
- 15 3. A method according to Claim 2 wherein said compound acting upon a mid-brain dopaminergic pathway is selected from the group consisting of apomorphine, bromocriptine, lisuride, methergoline, pergolide, pribidil and quinapril or a pharmaceutically acceptable salt, ester, or pro-drug thereof.
- 20 4. The method of Claim 1 wherein said compound acts upon a mid-brain serotonergic pathway
- 25 5. A method according to Claim 4 wherein said compound acting upon a mid-brain serotonergic pathway is selected from the group consisting of 1-(2,5-dimethoxy-4-iodophenyl)-1-aminopropane, 5-methoxytryptamine, α -methyl-5-hydroxytryptamine, 2-methyl-5-hydroxytryptamine, -acetyl-5-hydroxytryptamine, buspirone, and sumatriptin or a
30 pharmaceutically acceptable salt, ester, or pro-drug thereof.

-36-

6. The method of Claim 1 wherein said compound acts upon a mid-brain oxytocinergic pathway.

5 7. A method according to Claim 6 wherein said compound acting upon a mid-brain oxytocinergic pathway is selected from the group consisting of isotocin, carbetocin, Lys-conopressin, deaminoxytocin, mesotocin, antocin, glumitocin, aspargitocin, valitocin, asvatocin, phasvatocin, and seritocin or a pharmaceutically acceptable salt, ester,
10 or pro-drug thereof.

8. The method of Claim 1 wherein said compound acts upon a mid-brain nitroxidergic pathway.

15 9. The method according to Claim 8 wherein said compound acting upon a mid-brain nitroxidergic pathway is apomorphine or a pharmaceutically acceptable salt, ester, or pro-drug thereof.

20 10. A method of treating vasculogenic sexual dysfunction in a female in need of such treatment which comprises administering to a patient in need of such treatment a therapeutically effective amount of apomorphine or a pharmaceutically acceptable salt, ester, or pro-drug
25 thereof.

11. The method of Claim 10 wherein said apomorphine is co-administered with a apomorphine-potentiating effective amount of an androgen.

30

-37-

12. The method of Claim 11 wherein said androgen is selected from the group consisting of testosterone, dihydro-testosterone (DHT), dehydroepiandrosterone (DHEA), and pharmaceutically acceptable salts, esters and pro-drugs thereof.

13. The method of Claim 12 wherein said androgen is selected from testosterone and pharmaceutically acceptable salts, esters and pro-drugs thereof.

14. The method of Claim 11 wherein said apomorphine-potentiating effective amount of androgen and said apomorphine are chronically co-administered.

15. The method of Claim 11 wherein said apomorphine-potentiating amount of androgen and said apomorphine are co-administered on an as-needed basis.

16. The method of Claim 11 wherein said apomorphine-potentiating effective amount of androgen is administered prior to the administration of apomorphine.

17. The method of Claim 11 wherein said androgen is administered concomitantly with the administration of apomorphine.

18. A method of inducing effective vasocongestive arousal in a female in need of such treatment comprising administering a therapeutically effective amount of apomorphine or a pharmaceutically effective salt, ester, or pro-drug thereof.

19. The method of Claim 18 wherein said apomorphine is administered prior to sexual activity.

20. The method of Claim 18 wherein said apomorphine is co-administered with a apomorphine-potentiating effective amount of an androgen.

21. The method of Claim 20 wherein said androgen is selected from the group consisting of testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), and pharmaceutically acceptable salts, esters and pro-drugs thereof.

22. The method of Claim 21 wherein said androgen is selected from testosterone and pharmaceutically acceptable salts, esters and pro-drugs thereof.

23. The method of Claim 20 wherein said androgen is administered prior to the administration of apomorphine.

24. The method of Claim 14 wherein said androgen is administered concomitantly with the administration of apomorphine.

-39-

25. A method of treating vaginal engorgement insufficiency in a female in need of such treatment comprising administering a therapeutically effective amount of apomorphine or a pharmaceutically acceptable salt, ester or pro-drug thereof.

26. The method of Claim 25 wherein said apomorphine is administered prior to sexual activity.

27. The method of Claim 25 wherein said apomorphine is co-administered with a apomorphine-potentiating effective amount of an androgen.

28. The method of Claim 27 wherein said androgen is selected from the group consisting of testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), and pharmaceutically acceptable salts, esters and pro-drugs thereof.

29. The method of Claim 28 wherein said androgen is selected from testosterone and pharmaceutically acceptable salts, esters and pro-drugs thereof.

30. A method of treating clitoral erectile insufficiency in a female in need of such treatment comprising administering a therapeutically effective amount of apomorphine or a pharmaceutically acceptable salt, ester or pro-drug thereof.

31. The method of Claim 30 wherein said apomorphine is administered prior to sexual activity.

32. The method of Claim 30 wherein said apomorphine is co-administered with a apomorphine-potentiating effective amount of an androgen.

5 33. The method according to Claim 32 wherein said androgen is selected from the group consisting of testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), and pharmaceutically acceptable salts, esters and pro-drugs thereof.

10 34. The method of Claim 33 wherein said androgen is selected from testosterone and pharmaceutically acceptable salts, esters and pro-drugs thereof.

15 35. A method of treating vaginal pain comprising administering to a female in need of such treatment a compound which acts upon a dopaminergic, serotonergic, oxytocinergic or nitroxidergic mid-brain neural pathway to stimulate peripheral pelvic non-adrenergic non-cholinergic
20 (NANC) nerve cell release of nitric oxide (NO).

36. The method according to Claim 35 wherein said compound acts upon a mid-brain dopaminergic pathway.

25 37. The method of Claim 36 wherein said compound acting upon a mid-brain dopaminergic pathway is selected from the group consisting of apomorphine, bromocriptine, lisuride, methergoline, pergolide, pribidil and quinapril or a pharmaceutically acceptable salt, ester, or pro-drug
30 thereof.

-41-

38. The method of Claim 35 wherein said compound acts upon a serotonergic mid-brain pathway.

5 39. A method according to Claim 38 wherein said compound acting upon a mid-brain serotonergic pathway is selected from the group consisting of 1-(2,5-dimethoxy-4-iodophenyl)-1-aminopropane, 5-methoxytryptamine, α -methyl-5-hydroxytryptamine, 2-methyl-5-hydroxytryptamine, -acetyl-5-hydroxytryptamine, buspirone, and sumatriptin or a
10 pharmaceutically acceptable salt, ester, or pro-drug thereof.

40. The method according to Claim 35 wherein said compound acts upon an oxytocinergic mid-brain pathway.

15 41. A method according to Claim 40 wherein said compound acting upon a mid-brain oxytocinergic pathway is selected from the group consisting of isotocin, carbetocin, Lys-conopressin, deaminoxytocin, mesotocin, antocin, glumitocin, aspargitocin, valitocin, asvatocin, phasvatocin, and seritocin or a pharmaceutically acceptable salt, ester,
20 or pro-drug thereof.

25 42. The method of according to Claim 35 wherein said compound acts upon a nitroxidergic mid-brain pathway.

30 43. The method according to Claim 42 wherein said compound acting upon a mid-brain nitroxidergic pathway is apomorphine or a pharmaceutically acceptable salt, ester, or pro-drug thereof.

5 44. A method of treating vaginal pain in a female in need of such treatment which comprises administering to a patient in need of such treatment a therapeutically effective amount of apomorphine of a pharmaceutically acceptable salt, ester, or pro-drug thereof.

10 45. The method of Claim 44 wherein said apomorphine is co-administered with a apomorphine-potentiating effective amount of an androgen.

15 46. The method of Claim 45 wherein said androgen is selected from the group consisting of testosterone, Dehydrotestosterone (DHT), dehydroepiandrosterone (DHEA), and pharmaceutically acceptable salts, esters and pro-drugs thereof.

20 47. The method of Claim 46 wherein said androgen is testosterone or a pharmaceutically acceptable salt, ester, or pro-drug thereof.

25 48. The method of Claim 45 wherein said apomorphine-potentiating effective amount of androgen or said apomorphine is administered chronically.

30 49. The method of Claim 45 wherein said apomorphine-potentiating amount of androgen and said apomorphine are co-administered on an as-needed basis.

50. A method of treating dyspareunia in a female in need of such treatment comprising administering, in the interval between about 2 minutes and 120 minutes prior to coitus, a therapeutically effective amount of apomorphine or a pharmaceutically acceptable salt, ester, or pro-drug thereof.

51. The method of Claim 35 wherein said apomorphine is co-administered with a apomorphine-potentiating amount of an androgen.

52. The method of Claim 51 wherein said androgen is selected from the group consisting of testosterone, dihydrotestosterone (DHT), dehydroepiandrosterone (DHEA), and pharmaceutically acceptable salts, esters and pro-drugs thereof.

53. The method of Claim 52 wherein said androgen is selected from testosterone and pharmaceutically acceptable salts, esters and pro-drugs thereof.

54. The method of Claim 51 wherein said androgen is administered prior to the administration of apomorphine.

55. The method of Claim 51 wherein said androgen is administered concomitantly with the administration of apomorphine.

56. A method of diagnosing sexual dysfunction in a female patient comprising the steps of;

a) administering apomorphine or a pharmaceutically acceptable salt, ester, or pro-drug thereof; and

b) assessing a change in the physiological response in the patient to sexual activity, an improvement indicating sexual dysfunction in said patient.

57. The method of Claim 56 further comprising the co-administration of an androgen.

58. The method of Claim 57 wherein said androgen is testosterone or a pharmaceutically effective salt, ester, or pro-drug thereof.

1/10

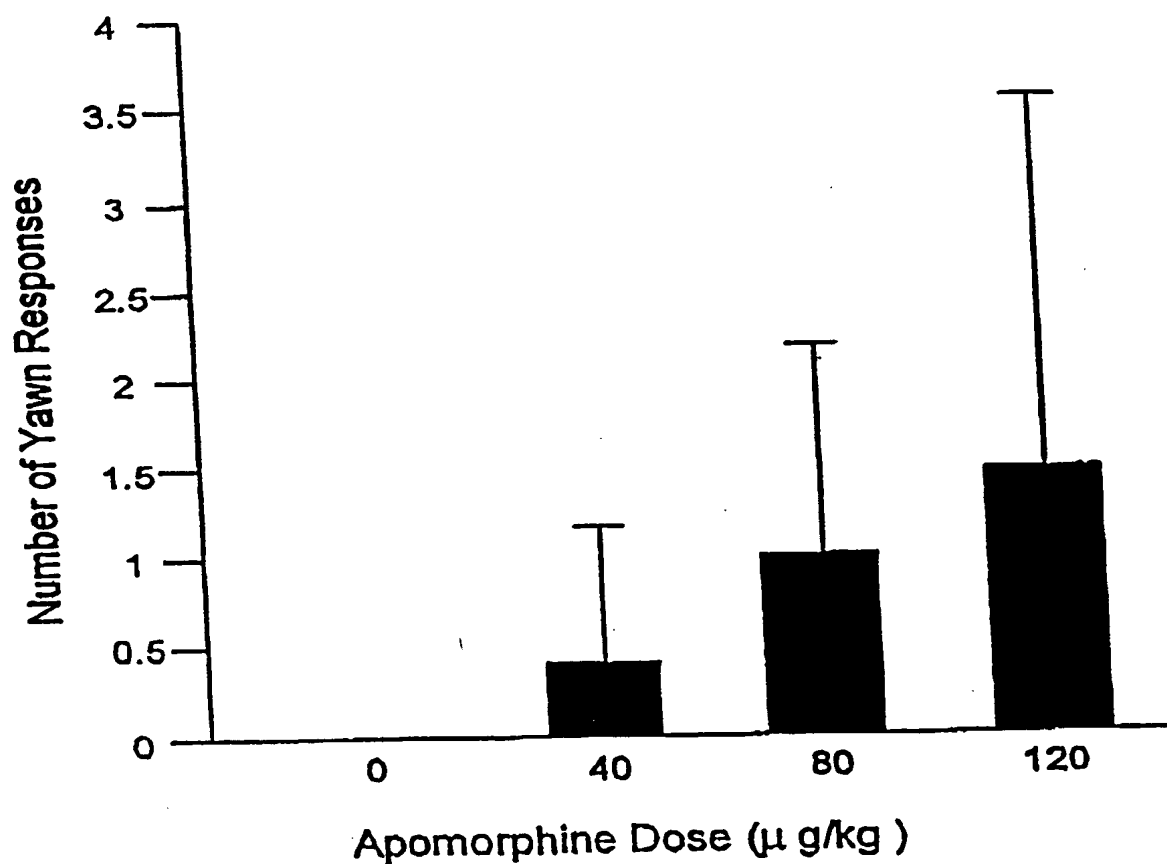


Figure 1

2/10

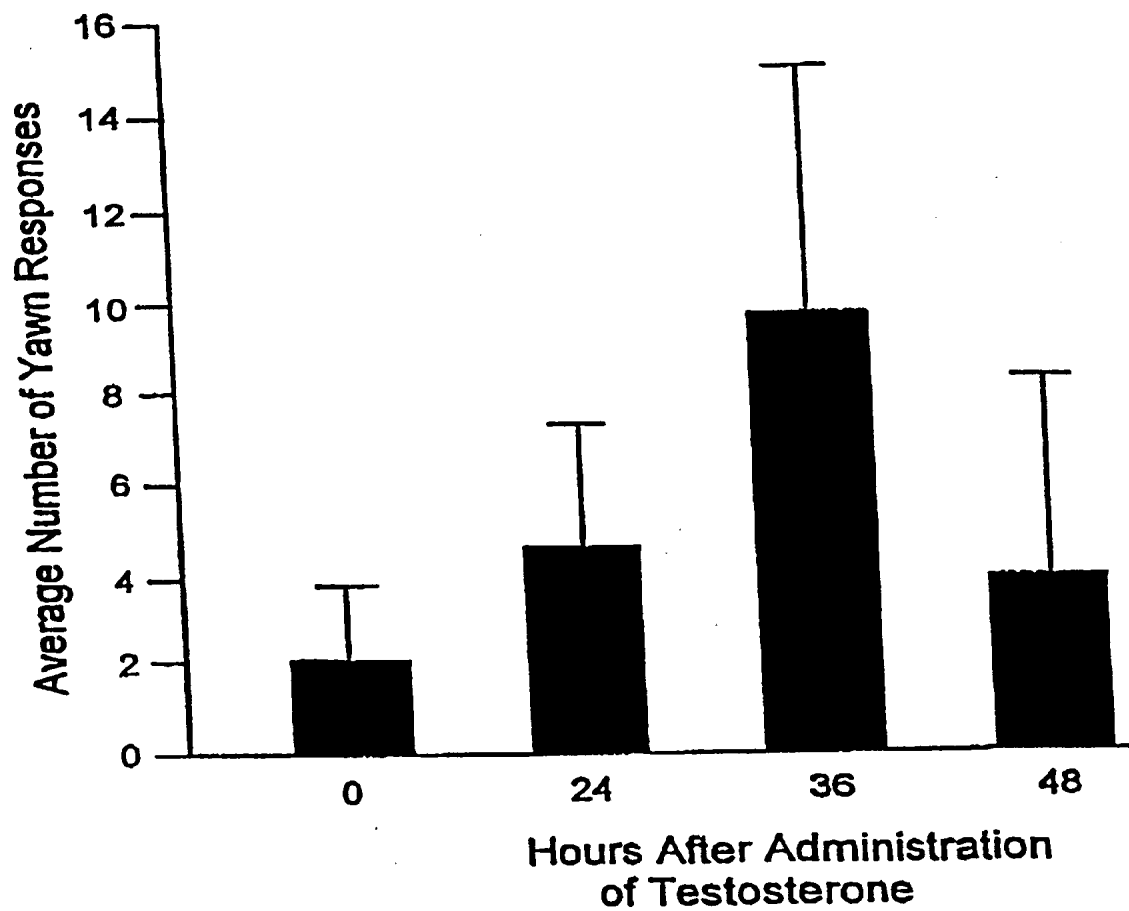
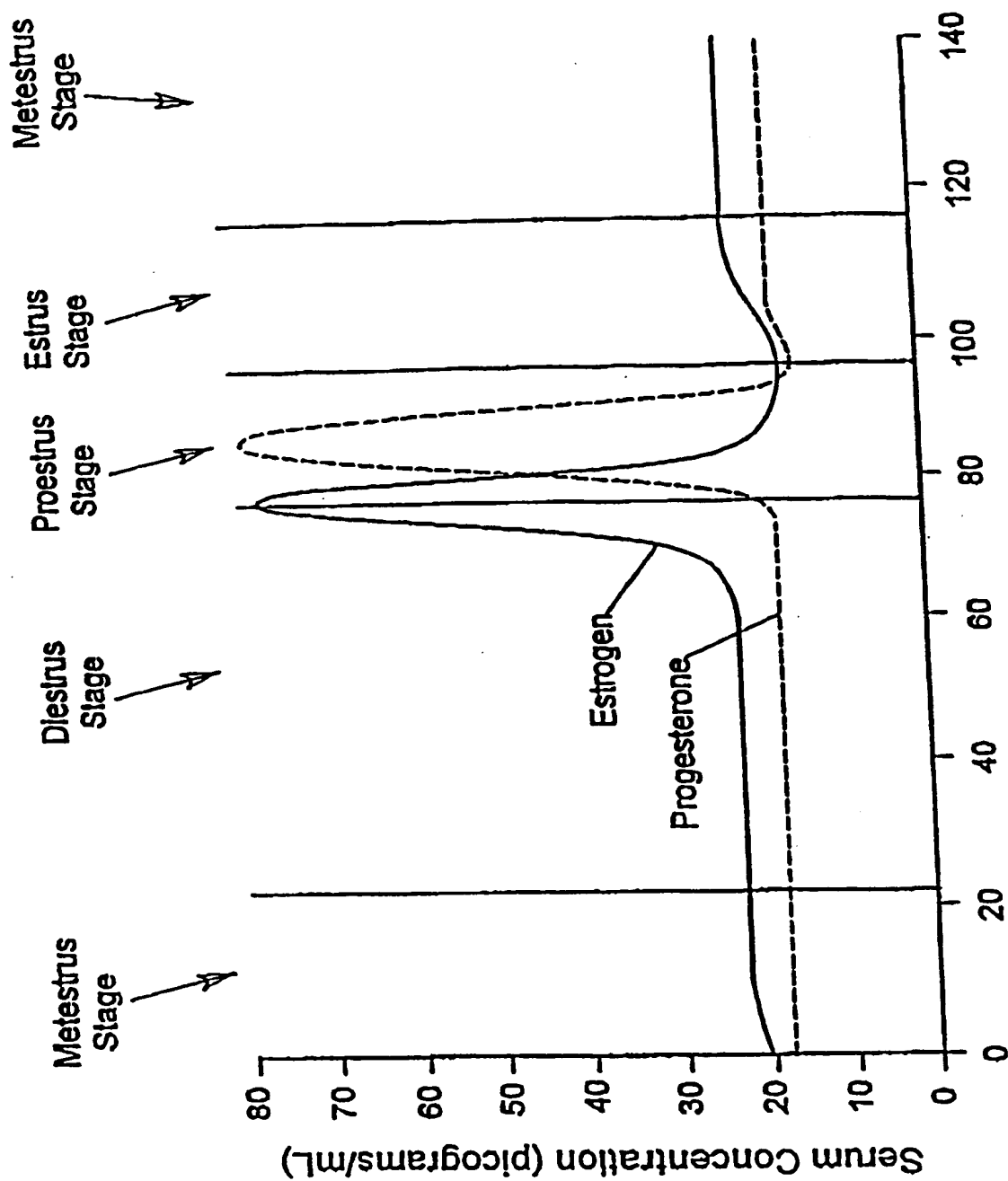


Figure 2

3/10



Female Rat Estrous Cycle (Hours)

Figure 3

4/10

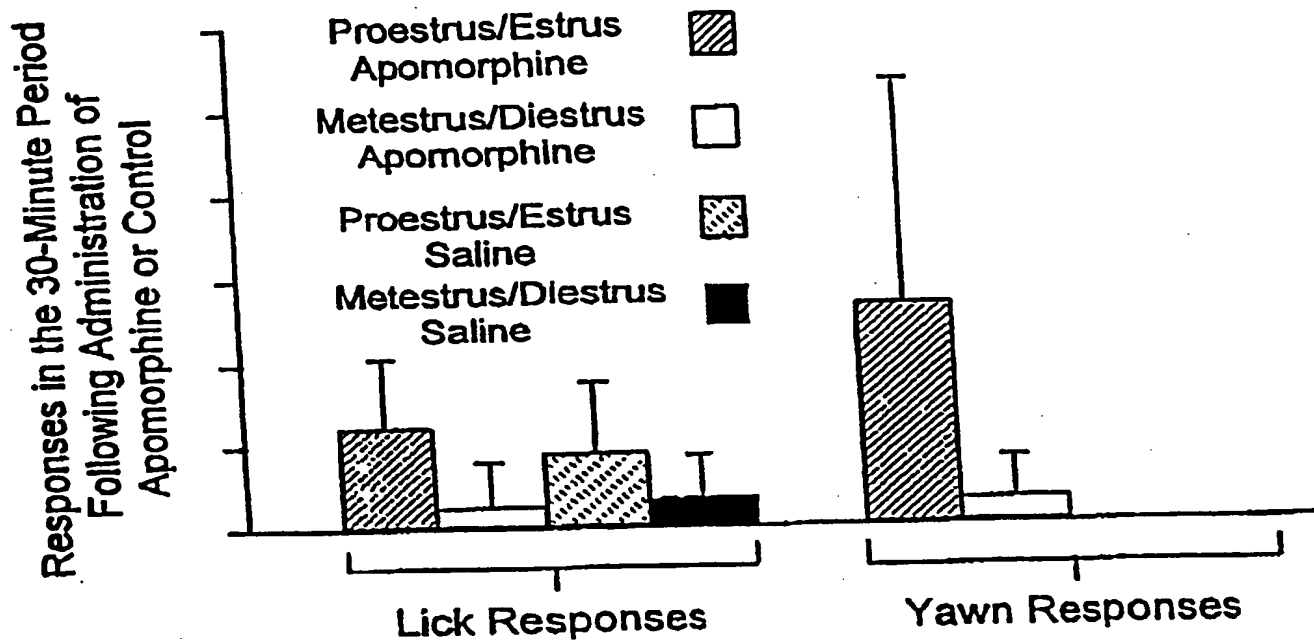


Figure 4

5/10

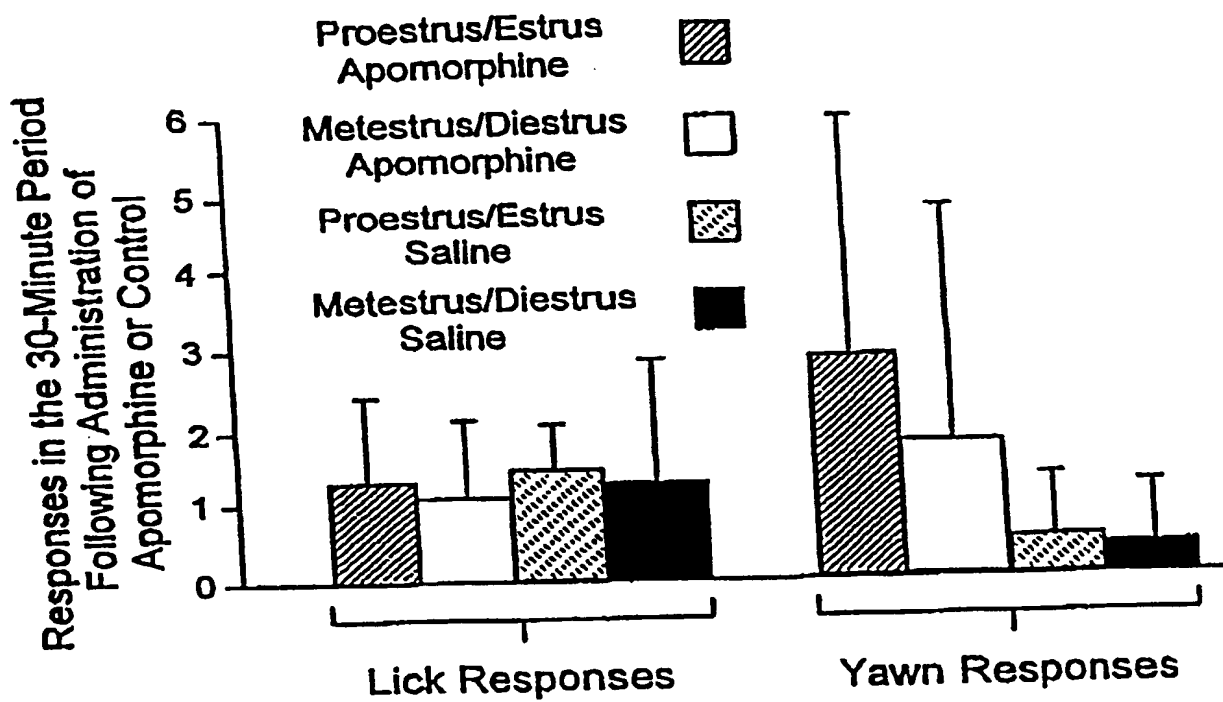


Figure 5

6/10

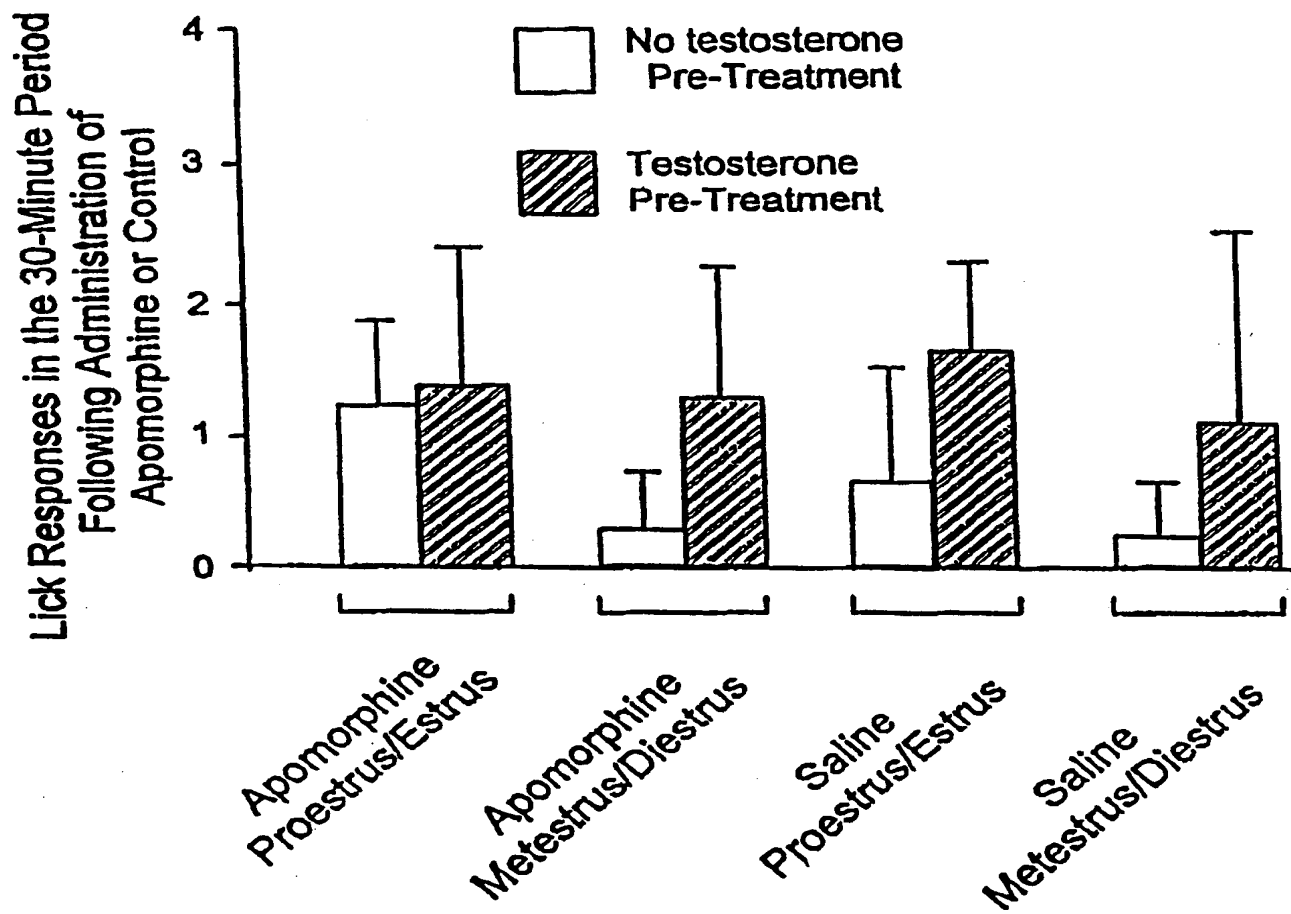


Figure 6

7/10

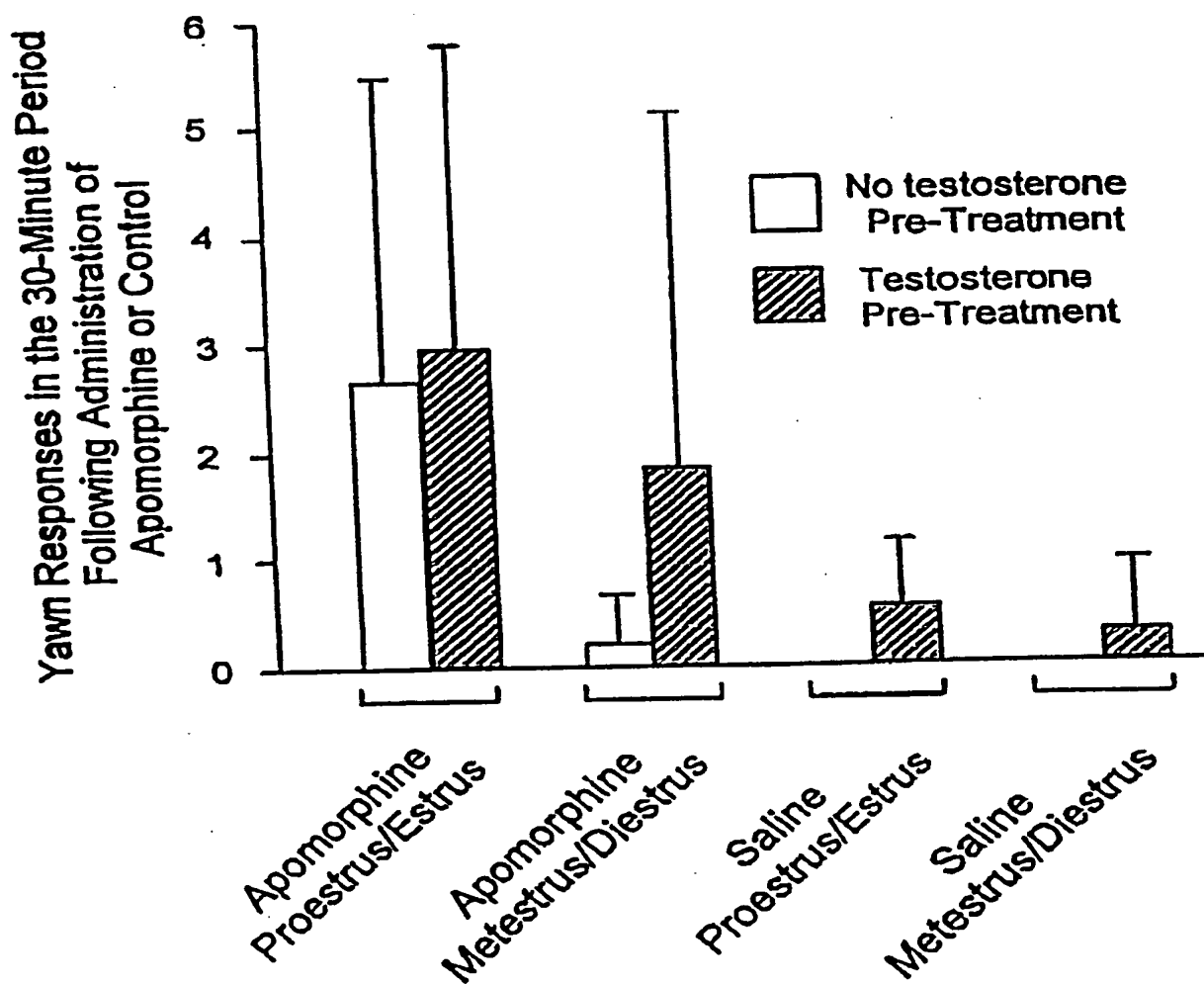


Figure 7

8/10

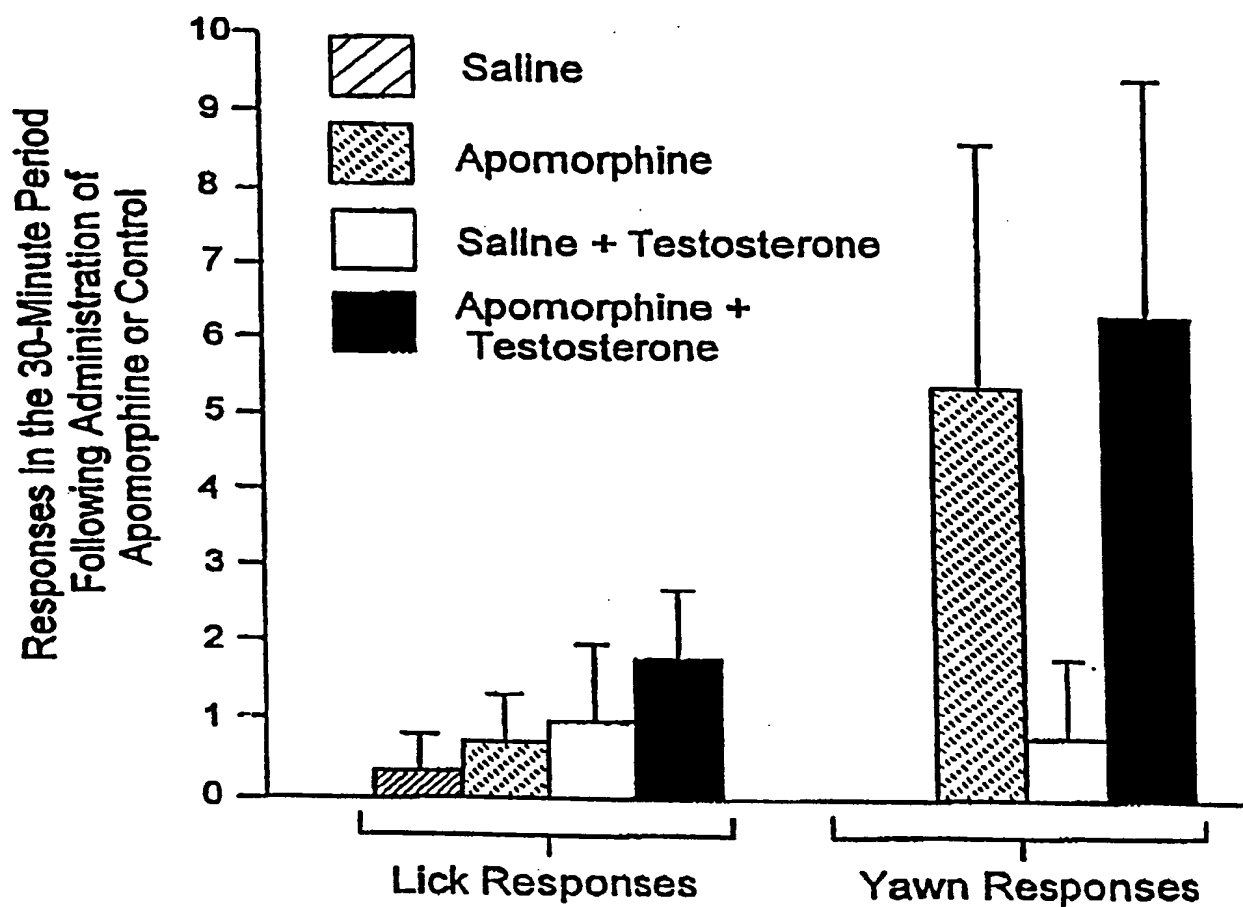


Figure 8

9/10

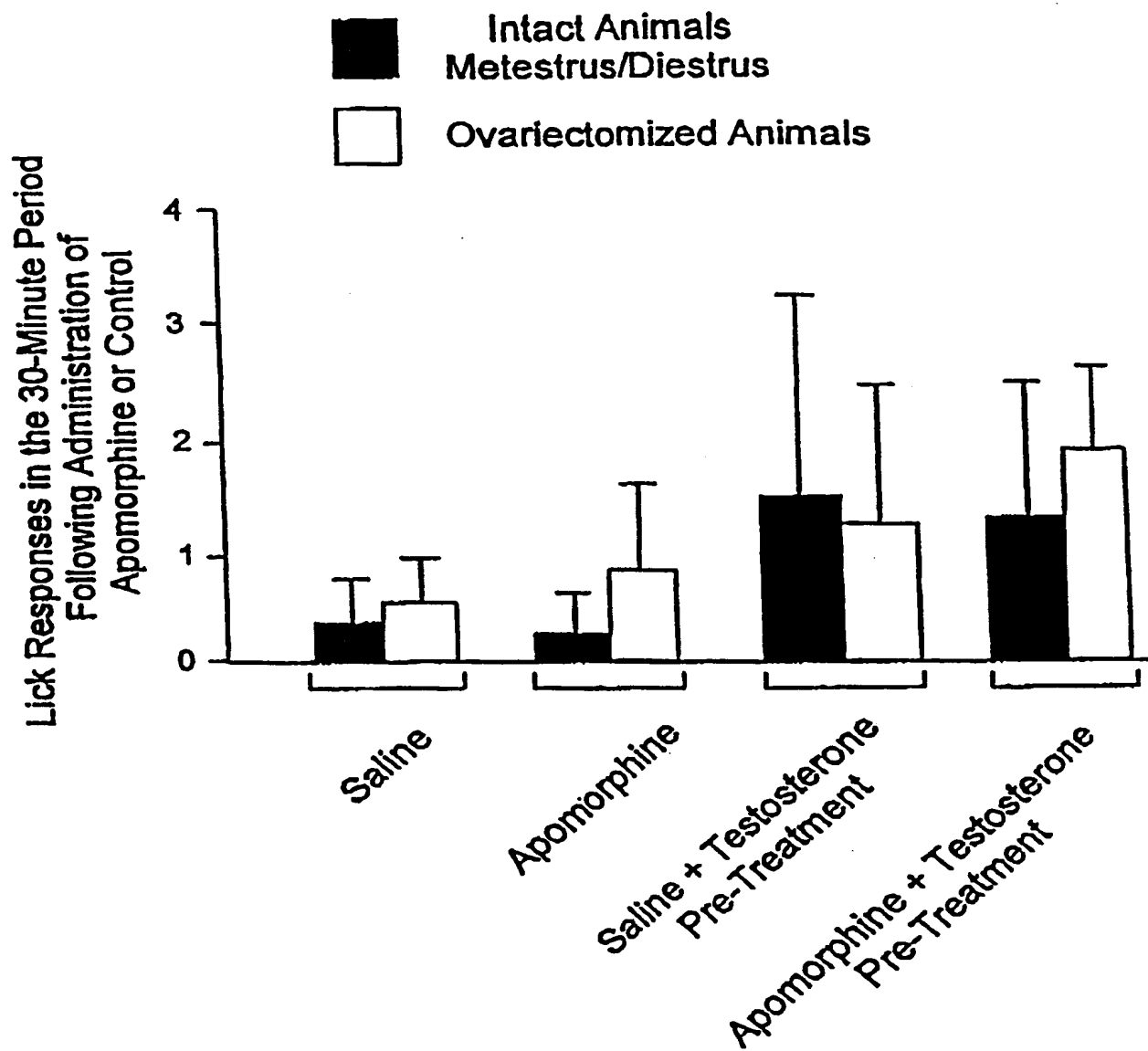


Figure 9

10/10

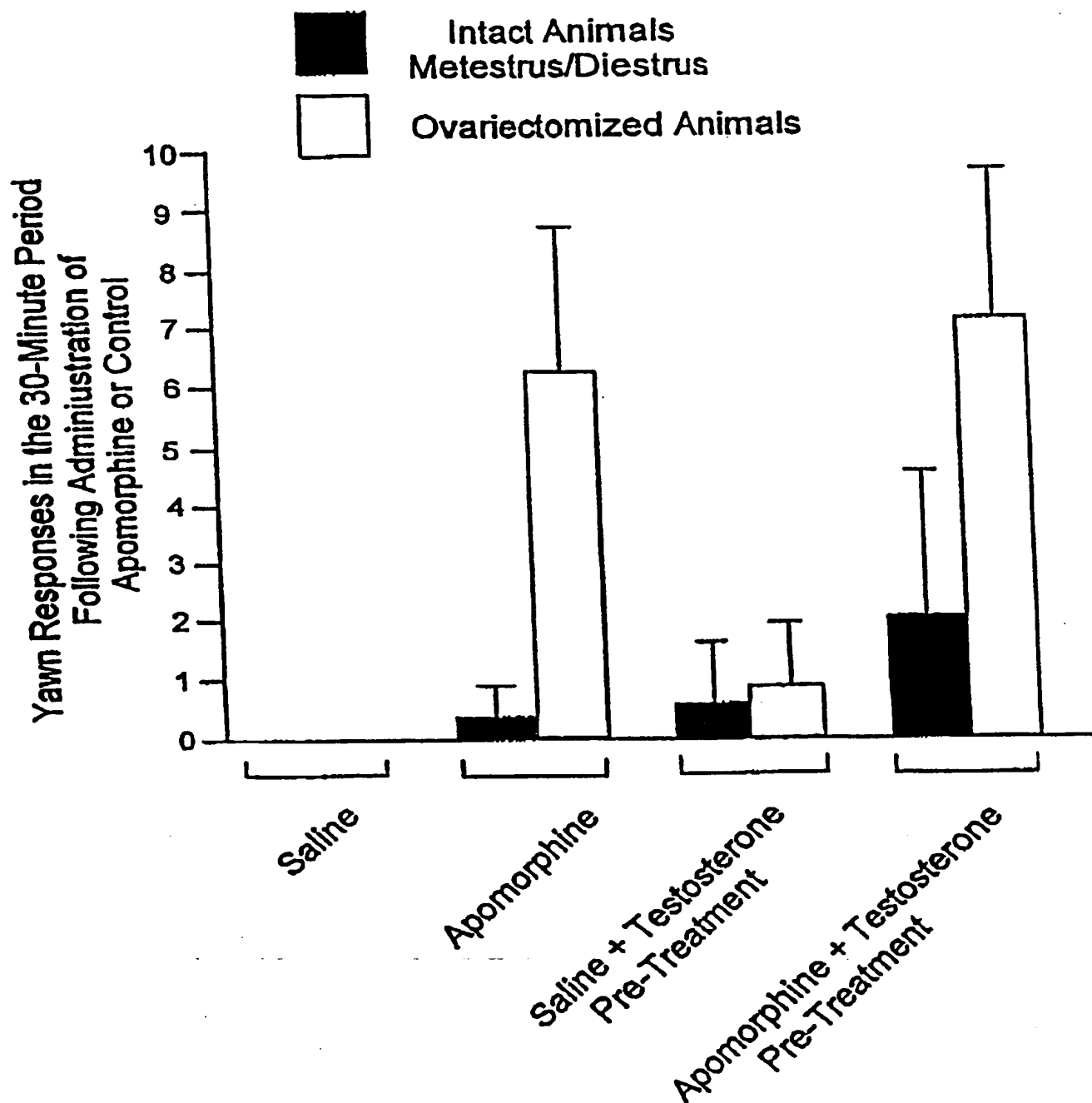


Figure 10



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/485, 31/47, 31/48, 31/505, 38/11, 38/12, 31/405, 31/40 // 31/565, 31:485		A3	(11) International Publication Number: WO 99/66909
			(43) International Publication Date: 29 December 1999 (29.12.99)
(21) International Application Number: PCT/CA99/00567		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 21 June 1999 (21.06.99)			
(30) Priority Data: 09/102,987 22 June 1998 (22.06.98) US			
(63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 09/102,987 (CIP) Filed on 22 June 1998 (22.06.98)		Published With international search report.	
1) Applicant (for all designated States except US): QUEEN'S UNIVERSITY AT KINGSTON [CA/CA]; Kingston, Ontario K7L 3N6 (CA).		(88) Date of publication of the international search report: 29 June 2000 (29.06.00)	
(72) Inventors; and (75) Inventors/Applicants (for US only): ADAMS, Michael, A. [CA/CA]; 341 Renda Street, Kingston, Ontario K7M 5X9 (CA). HEATON, Jeremy, P., W. [CA/CA]; 1818 MacAlpine Road, R.R. #3, Gananoque, Ontario K7G 2V7 (CA).			
(74) Agents: STEEG, Carol, Miernicki et al.; Parteq Innovations, Queen's University at Kingston, Kingston, Ontario K7L 3N6 (CA).			

(54) Title: METHOD AND COMPOSITIONS FOR THE TREATMENT OR AMELIORATION OF FEMALE SEXUAL DYSFUNCTION

(57) Abstract

The present invention provide a method of treating sexual dysfunction in a female, including the vasculogenic symptoms of delayed vaginal engorgement, diminished vaginal lubrication, pain or discomfort with intercourse (dyspareunia), diminished vaginal sensation, diminished clitoral orgasm, or of combating vaginal pain. The preferred compound for the method of this invention is apomorphine or one of its pharmaceutically acceptable salts, esters, or pro-drugs. Other compounds are selected from the group consisting of (i) bromocriptine, ergotamine, methergolide, pergolide, prigidil, guinapril; or (ii) 1-(2,5-dimethoxy-4-iodophenyl)-1-aminopropane, 5-methoxytryptamine, alpha-methyl-5-hydroxytryptamine, 2-methyl-5-hydroxytryptamine, N-acetyl-5-hydroxytryptamine, buspirone, sumatriptan; or (iii) isotocin, carbetocin, lysconopressin, deaminoxytocin, mesotocin, antocin, glutitocin, aspartitocin, valitocin, asvatocin, phasvatocin and seritocin. Alternatively, the apomorphine is co-administered with an apomorphine-potentiating amount of androgen, preferably testosterone either prior to, or concomitantly with, the administration of the apomorphine.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

INTERNATIONAL SEARCH REPORT

Inter national Application No
PCT/CN/00567

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/485 A61K31/47 A61K31/48 A61K31/505 A61K38/11
A61K38/12 A61K31/405 A61K31/40 //A61K31/565,
31:485

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 23035 A (SMITHKLINE BEECHAM PLC ;FEARS ROBIN BRADSHAW (GB)) 25 November 1993 (1993-11-25) abstract page 2, line 18-25; claims 3,6 ---	1,2
X	US 4 521 521 A (ABBOTT SCOT D ET AL) 4 June 1985 (1985-06-04) abstract column 9, line 46-58 column 18, line 29-69; claims 1,6; tables 4,5 ---	1-3, 8-37, 42-55
X	EP 0 172 697 A (LILLY CO ELI) 26 February 1986 (1986-02-26) abstract page 39, line 20-24 ---	1,2
-/--		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

15 November 1999

Date of mailing of the international search report

3 0. 03 00

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

A. Jakobs

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/CA 00567

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 87 04621 A (OTHMER EKKEHARD ;OTHMER SIEGLINDE C (US)) 13 August 1987 (1987-08-13) --- abstract page 4, line 30 -page 5, line 11 page 10, line 13 -page 11, line 29	4,5
X	GOLDSTEIN I. ET AL: "Vasculogenic female sexual dysfunction: Vaginal engorgement and clitoral erectile insufficiency syndromes." INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH, (1998) 10/SUPPL. 2 (S84-S90)., XP002121200 abstract page S89, column 1, paragraph 5 -page S89, column 2	1-3, 8-37, 42-55
X	SEGRAVES R.T. ET AL: "Pharmacotherapy for sexual disorders: Advantages and pitfalls." SEXUAL AND MARITAL THERAPY, (1998) 13/3 (295-309)., XP002121201 page 299, paragraph 2	1-3, 8-37, 42-55
X	FERRARI, F. ET AL: "Influence of apomorphine on rat female sexual behavior and its relation with induction of stereotypy" RIV. FARMACOL. TER. (1977), 8(4), 355-63, XP002121202 abstract page 357, paragraph 5 -page 362, paragraph 1; tables 1-3	1-3, 8-37, 42-55
X	MELIS M.R. ET AL: "Dopamine and sexual behavior." NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS, (1995) 19/1 (19-38)., XP002121203 abstract; table 13	1-3, 8-37, 42-55
X	HAMBURGER-BAR, R.; RIGTER, H.: "Apomorphine: Facilitation of sexual behaviour in female rats" EUROPEAN JOURNAL OF PHARMACOLOGY, XP002121204 cited in the application abstract; figure 1; table 1 page 358, column 2, paragraph 3 -page 359, column 2, paragraph 5	1-3, 8-37, 42-58
E	US 5 945 117 A (RONSEN BRUCE ET AL) 31 August 1999 (1999-08-31) the whole document	1-3, 8-37, 42-55

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/CA 99/00567

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
present claims
3. ☐ Claims Nos.
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Claims: 1-3, 8, 35-37, 42(partially) 9-34, 43-55, 56-58

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-55 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition as relating to invention 1 as defined.

Although claims 56-58 are directed to a diagnostic method practised on the human/animal body, the search would be carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Present claims

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ CA 99 / 00567

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

1. Claims: 1-3,8,35-37,42(partially)9-34,43-55, 56-58

Use of apomorphine for treating sexual dysfunction in a female mammal, inducing vasocongestive arousal in a female, treating vaginal engorgement insufficiency in a female, treating clitoral erectile insufficiency in a female, treating vaginal pain, treating dyspareunia in a female and use of apomorphine for diagnosing sexual dysfunction by assessing a change in the physiological response in the patient to sexual activity, an improvement indicating sexual dysfunction in said patient.

2. Claims: 1-3,35-37 (partially)

Use of a compound selected from the group consisting of bromocriptine, lisuride, methergolide, pergolide and quinapril for treating sexual dysfunction in a female mammal, and treating vaginal pain in a female.

3. Claims: 1,4,5,35-39(partially)

Use of 1-(2,5-dimethoxy-4-iodophenyl)-1-aminopropane for treating sexual dysfunction in a female mammal, and treating vaginal pain in a female.

4. Claims: 1,4,5,35-39(partially)

Use of a compound selected from the group consisting of 5-methoxytryptamine, alpha-methyl-5-hydroxytryptamine, 2-methyl-5-hydroxytryptamine, N-acetyl-5-hydroxytryptamine and sumatriptan for treating sexual dysfunction in a female mammal, and treating vaginal pain in a female.

5. Claims: 1,4,5,35-39(partially)

Use of Buspirone for treating sexual dysfunction in a female mammal, and treating vaginal pain in a female.

6. Claims: 1,35(partially),6,7,40,41

Use of isotocin, carbetocin, lysconopressin, deaminoxytocin, mesotocin, antocin, glutitocin, aspargitocin, valitocin, asvatocin, phasvatocin and seritocin for treating sexual dysfunction in a female mammal, and treating vaginal pain in a female.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No
PCT/CA 00567

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9323035 A	25-11-1993	AU 4312593 A EP 0641202 A JP 7506823 T	13-12-1993 08-03-1995 27-07-1995
US 4521521 A	04-06-1985	CA 1208938 A DK 146884 A EP 0118894 A GR 81840 A JP 59173759 A	05-08-1986 12-09-1984 19-09-1984 12-12-1984 01-10-1984
EP 0172697 A	26-02-1986	AR 240822 A AT 67766 T AU 569406 B AU 4573785 A CA 1292742 A DE 3584205 A DK 349185 A ES 545859 D ES 8704499 A ES 551964 D ES 8800231 A GR 851895 A HU 193338 B HU 38348 A IE 58695 B JP 6070063 B JP 61047487 A KR 8801430 B NZ 212946 A PH 22541 A PT 80899 A,B SU 1421258 A ZA 8505830 A	28-02-1991 15-10-1991 28-01-1988 06-02-1986 03-12-1991 31-10-1991 03-02-1986 01-04-1987 16-06-1987 16-10-1987 01-01-1988 03-12-1985 28-09-1987 28-05-1986 03-11-1993 07-09-1994 07-03-1986 08-08-1988 28-07-1988 17-10-1988 01-09-1985 30-08-1988 25-03-1987
WO 8704621 A	13-08-1987	US 4640921 A AU 7164987 A	03-02-1987 25-08-1987
US 5945117 A	31-08-1999	AU 2564499 A WO 9938467 A	16-08-1999 05-08-1999